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Commissioner for Patents  
Washington, D.C. 20231

Re: U.S. Patent Application No.: 09/914451  
For: *DRUG DESIGN BASED ON THE STRUCTURE OF LTA<sub>4</sub> HYDROLASE*  
Inventors: Jesper Z. Haeggström *et al.*  
Filed: August 27, 2001  
Our Ref. No.: PVZ-006US

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Information Disclosure Statement;
2. PTO Form 1449;
3. Copies of references cited in PTO Form 1449 (43); and
4. A Return Postcard.

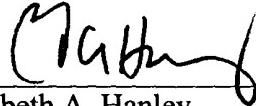
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Elizabeth A. Hanley, Reg. No. 33,505

Respectfully submitted,  
LAHIVE & COCKFIELD, LLP

  
Elizabeth A. Hanley  
Registration No. 33,505  
Attorney for Applicants



23 2002  
23595  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Jesper Z. Haeggström *et al.*

Serial No.: 09/914451

Filed: August 27, 2001

For: *DRUG DESIGN BASED ON THE STRUCTURE  
OF LTA<sub>4</sub> HYDROLASE*

Attorney Docket No.: PVZ-006US

Group Art Unit: 1642

Examiner: Not yet assigned

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By:

  
Elizabeth A. Hanley  
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Attorney for Applicants

Date of Signature and of Mail Deposit

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicants and their Attorney are aware of the following publications and information, listed on the attached PTO Form 1449, and in accordance with 37 CFR §1.97 hereby submit these publications for the Examiner's consideration. A copy of each cited publication is enclosed.

This statement is not to be interpreted as a representation that the cited publications are material, that an exhaustive search has been conducted, or that no other

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relevant information exists. Nor shall the citation of any publication herein be construed *per se* as a representation that such publication is prior art. Moreover, Applicants understand that the Examiner will make an independent evaluation of the cited publications.

Under 37 C.F.R. § 1.97(b)(3), no additional costs are believed to be due in connection with the filing of this disclosure. If, however, a first Office Action on the merits issues in this application bearing a mailing date prior to the date of this Information Disclosure Statement, please charge the appropriate fee as required under 37 CFR §1.17(p) to our Deposit Order Account No. 12-0080.

Respectfully submitted,  
LAHIVE & COCKFIELD, LLP



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Date: 12/19/02

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09/914451

**LIST OF PUBLICATIONS CITED BY APPLICANT**  
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Jesper Z. Haeggström et al.

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## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO

## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

A1	Andberg, M. et al. "Mutation of tyrosine 383 in leukotriene A <sub>4</sub> hydrolase allows conversion of leukotriene A <sub>4</sub> into 5S,6S-dihydroxy-7,9-trans-11,14-cis-eicosatetraenoic acid. Implications for the epoxide hydrolase mechanism," <i>J. Biol. Chem.</i> 1997 Sep 12;272(37):23057-63
A2	Barrett, A.J. et al. Eds. "336. Introduction: family M1 of membrane alanyl aminopeptidase," in <i>Handbook of proteolytic enzymes</i> 1998 Oct; pp. 994-996
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A4	Byrum, R.S. et al. "Determination of the contribution of cysteinyl leukotrienes and leukotriene B <sub>4</sub> in acute inflammatory responses using 5-lipoxygenase- and leukotriene A <sub>4</sub> hydrolase-deficient mice," <i>J. Immunol.</i> 1999 Dec 15;163(12):6810-9
A5	Chen, X.-S. et al. "Role of leukotrienes revealed by targeted disruption of the 5-lipoxygenase gene," <i>Nature</i> 1994 Nov;372:179-182
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A7	Devchand, P.R. et al. "The PPARalpha-leukotriene B <sub>4</sub> pathway to inflammation control," <i>Nature</i> 1996 Nov 7;384(6604):39-43
A8	Dittmann, K.H. et al. "MK-886, a leukotriene biosynthesis inhibitor, induces antiproliferative effects and apoptosis in HL-60 cells," <i>Leuk. Res.</i> 1998 Jan;22(1):49-53
A9	Drazen, J.M. et al. "Treatment of asthma with drugs modifying the leukotriene pathway," <i>N. Engl. J. Med.</i> 1999 Jan 21;340(3):197-206
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A11	Ford-Hutchinson, A.W. et al. "Leukotriene B, a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes," <i>Nature</i> 1980 July 17;286:264-65
A12	Funk, C.D. et al. "Molecular cloning and amino acid sequence of leukotriene A <sub>4</sub> hydrolase," <i>Proc. Natl. Acad. Sci. USA</i> 1987 Oct;84(19):6677-81
A13	Griffiths, R.J. et al. "Leukotriene B <sub>4</sub> plays a critical role in the progression of collagen-induced arthritis," <i>Proc. Natl. Acad. Sci. USA</i> 1995 Jan 17;92(2):517-21
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Examiner

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Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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**FOREIGN PATENT DOCUMENTS**

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION
					YES	NO	

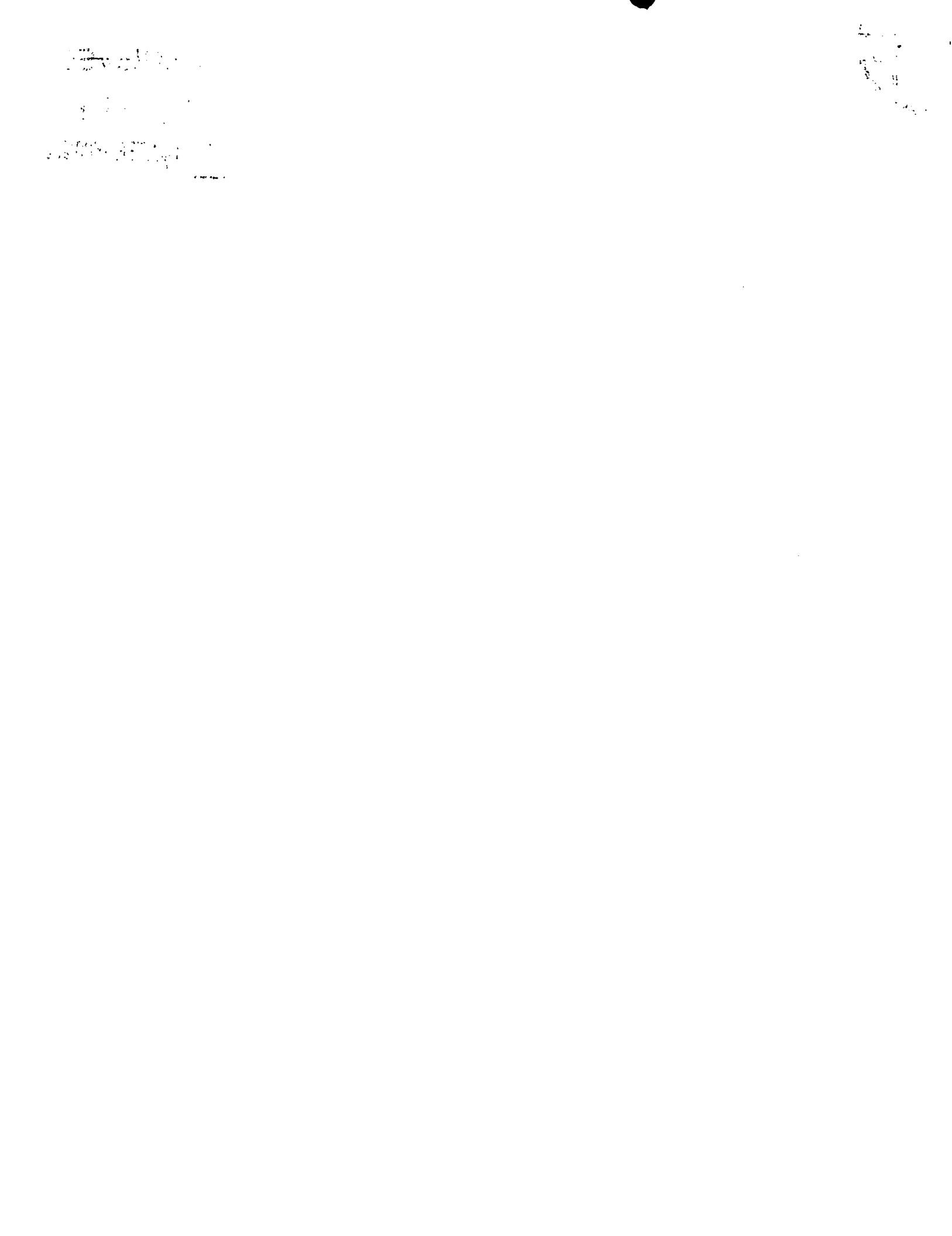
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B1	Haeggström, J.Z. et al. "Leukotriene A <sub>4</sub> hydrolase: structural and functional properties of the active center," <i>J. Lipid Mediat.</i> 1993 Mar-Apr;6(1-3):1-13
B2	Hogg, J.H. et al. "Probing the activities and mechanisms of leukotriene A <sub>4</sub> hydrolase with synthetic inhibitors," <i>Chem. Eur. J.</i> 1998;4(9):1698-1713
B3	Kuchner, O. et al. "Directed evolution of enzyme catalysts," <i>Trends Biotechnol.</i> 1997 Dec;15(12):523-30
B4	Labaudinière, R. et al. "ω -[(ω-Arylalkyl)thienyl]alkanoic acids: from specific LTA <sub>4</sub> hydrolase inhibitors to LTB <sub>4</sub> receptor antagonists," <i>J. Med. Chem.</i> 1992 Aug 21;35(17):3170-9
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B7	Medina, J.F. et al. "Leukotriene A <sub>4</sub> hydrolase: determination of the three zinc-binding ligands by site-directed mutagenesis and zinc analysis," <i>Proc. Natl. Acad. Sci. USA</i> 1991 Sep 1;88(17):7620-4
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B9	Mueller, M.J. et al. "Leukotriene A <sub>4</sub> hydrolase: mapping of a heicosapeptide involved in mechanism-based inactivation," <i>Proc. Natl. Acad. Sci. USA</i> 1995 Aug 29;92(18):8383-7
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B11	Mueller, M.J. et al. "Leukotriene A <sub>4</sub> hydrolase, mutation of tyrosine 378 allows conversion of leukotriene A <sub>4</sub> into an isomer of leukotriene B <sub>4</sub> ," <i>J. Biol. Chem.</i> 1996 Oct 4;271(40):24345-8
B12	Nord, K. et al. "Binding proteins selected from combinatorial libraries of an alpha-helical bacterial receptor domain," <i>Nat. Biotechnol.</i> 1997 Aug;15(8):772-7
B13	Orning, L. et al. "Inhibition of leukotriene A <sub>4</sub> hydrolase/aminopeptidase by captopril," <i>J. Biol. Chem.</i> 1991 Sep 5;266(25):16507-11
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LIST OF PUBLICATIONS CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT <b>Jesper Z. Ha ggstr"m et al.</b>	<b>RECEIVED</b>
		FILING DATE <b>August 27, 2001</b>	GROUP <b>1642 DEC 27 2002</b>

## U. S. PATENT DOCUMENTS

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## FOREIGN PATENT DOCUMENTS

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## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

C1	Owman, C. et al. "The leukotriene B <sub>4</sub> receptor functions as a novel type of coreceptor mediating entry of primary HIV-1 isolates into CD4-positive cells," <i>PNAS. USA</i> 1998 Aug 4;95(16):9530-4
C2	Rola-Pleszczynski, M. et al. "Leukotrienes augment interleukin 1 production by human monocytes," <i>J. Immunol.</i> 1985 Dec;135(6):3958-61
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C4	Samuelsson, B. et al. "Leukotrienes and lipoxins: structures, biosynthesis, and biological effects," <i>Science</i> 1987 Sep 4;237(4819):1171-6
C5	Serhan, C.H. et al. "Lipid mediator networks in cell signaling: update and impact of cytokines," <i>FASEB J.</i> 1996 Aug;10:1-12
C6	Tsuge, H. et al. "Crystallization and preliminary X-ray crystallographic studies of recombinant human leukotriene A <sub>4</sub> hydrolase complexed with bestatin," <i>J. Mol. Biol.</i> 1994 May 20;238(5):854-6
C7	Vallee, B.L. et al. "Active-site zinc ligands and activated H <sub>2</sub> O of zinc enzymes," <i>Proc. Natl. Acad. Sci. USA</i> 1990 Jan;87(1):220-4
C8	Wetterholm, A. et al. "Recombinant mouse leukotriene A <sub>4</sub> hydrolase: a zinc metalloenzyme with dual enzymatic activities," <i>Biochim. Biophys. Acta</i> 1991 Oct 25;1080(2):96-102
C9	Wetterholm, A. et al. "Leukotriene A <sub>4</sub> hydrolase: abrogation of the peptidase activity by mutation of glutamic acid-296," <i>Proc. Natl. Acad. Sci. USA</i> 1992 Oct 1;89(19):9141-5
C10	Wetterholm, A. et al. "Potent and selective inhibitors of leukotriene A <sub>4</sub> hydrolase: effects on purified enzyme and human polymorphonuclear leukocytes," <i>J. Pharmacol. Exp. Ther.</i> 1995 Oct;275(1):31-7
C11	Yamaoka, K.A. et al. "Leukotriene B <sub>4</sub> enhances activation, proliferation, and differentiation of human B lymphocytes," <i>J. Immunol.</i> 1989 Sep 15;143(6):1996-2000
C12	Yokomizo, T. et al. "A G-protein-coupled receptor for leukotriene B <sub>4</sub> that mediates chemotaxis," <i>Nature</i> 1997 Jun 5;387(6633):620-4
C13	Yokomizo, T. et al. "A second leukotriene B <sub>4</sub> receptor, BLT2. A new therapeutic target in inflammation and immunological disorders," <i>J. Exp. Med.</i> 2000 Aug 7;192(3):421-32
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C15	GenPept Acc. No. S65947; leukotriene-A4 hydrolase (EC 3.3.2.6) long isoform - human
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